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   G.1344

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   ELI LILLY AND COMPANY LIMITED,
   KINGSCLERE ROAD,
   BASINGSTOKE,
   HAMPSHIRE RG21 6XA

   Patents ADP number *(if you know it)*

   ~~6106002~~

   If the applicant is a corporate body, give the country/state of its incorporation

   GREAT BRITIAN

   07755291001

4. Title of the invention

   PHARMACEUTICAL COMPOUNDS

5. Name of your agent *(if you have one)*

   C. M. HUDSON

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   LILLY RESEARCH CENTRE,
   ERL WOOD MANOR,
   WINDLESHAM,
   SURREY GU20 6PH

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

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12. Name and daytime telephone number of person to contact in the United Kingdom MR. C. M. HUDSON (01276) 853443

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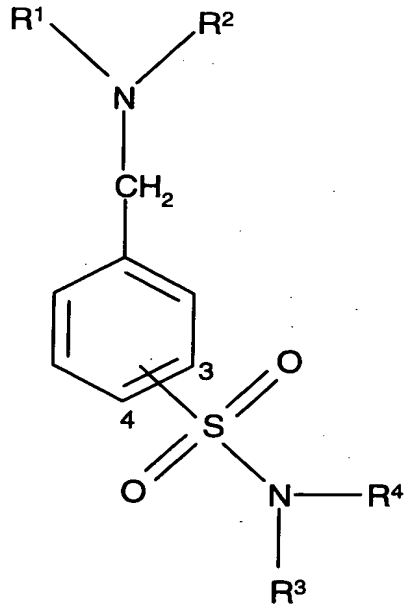
PHARMACEUTICAL COMPOUNDS

This invention relates to novel chemical compounds and their use as pharmaceuticals.

It is well known that chemical compounds which modulate the activity of neuronal calcium channels are potentially useful in treating disorders of the central nervous system.

The compounds of the invention have the following general formula:



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being

optionally fused to an optionally substituted phenyl group;

or a salt thereof.

The compounds of the invention have been found to be active in tests that show modulation of voltage-dependent calcium channels, and are thus indicated for use in the treatment of diseases in which such modulation is beneficial, in particular diseases of the central nervous system.

In the above formula (I), a C_{1-6} alkyl group includes methyl, ethyl, propyl, isopropyl, butyl, tert. butyl and hexyl, and is preferably methyl or ethyl. A substituted phenyl group is phenyl substituted with one or more, for example one to three, substituents selected from, for example C_{1-4} alkyl, especially methyl, C_{1-4} alkoxy, especially methoxy and ethoxy, hydroxy, nitro, cyano, halo, especially chloro or fluoro, trihalomethyl, especially trifluoromethyl, carboxy and C_{1-4} alkoxy-carbonyl. A halo atom is preferably chlorine, bromine or fluorine. A substituted phenyl group preferably has one to three substituents selected from hydroxy, C_{1-4} alkyl, halo, nitro and trifluoromethyl. An optionally

substituted phenyl-C_{1-4} alkyl group is preferably of the formula R-$(CH_2)_n$- where R is optionally substituted phenyl and n is 1 to 4, but the linking chain can also be branched alkylene. A C_{3-10} cycloalkyl group is preferably, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and these groups may optionally be substituted by one or two C_{1-4} alkyl, especially methyl, substituents. A C_{3-10} cycloalkyl-C_{1-4} alkyl group is one such cycloalkyl group attached to a C_{1-4} alkyl, and is preferably of the formula R-$(CH_2)_n$- where R is cycloalkyl and n is 1 to 4. When R^3 or R^4 is C_{1-6} alkyl it is preferably C_{3-6} alkyl.

The groups R^1 and R^2, R^3 and R^4, and R^5 and R^6, can form a carbocyclic ring with the nitrogen to which they are attached and optionally also contain an oxygen atom or an additional nitrogen. Preferred examples, including the nitrogen of the amino sulfonyl group, are pyrrolidino, piperazino, morpholino and especially 3,5-dimethylpiperidino.

A particular group of compounds of the invention is one of formula (I) in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or

optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with the nitrogen atom to which they are attached, form a carbocyclic group as defined above.

In a preferred group of compounds R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 is in addition hydrogen.

It is preferred that R^1 is hydrogen. Furthermore, R^3 and R^4, which can be the same or different, are preferably C_{1-4} alkyl. It is further preferred that R^2 is optionally substituted phenyl-C_{1-4} alkyl.

A further preferred group of compounds is one of formula (I) in which R^2 is $-(CH_2)_2NR^5R^6$.

A further preferred group of compounds is one of formula (I) in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

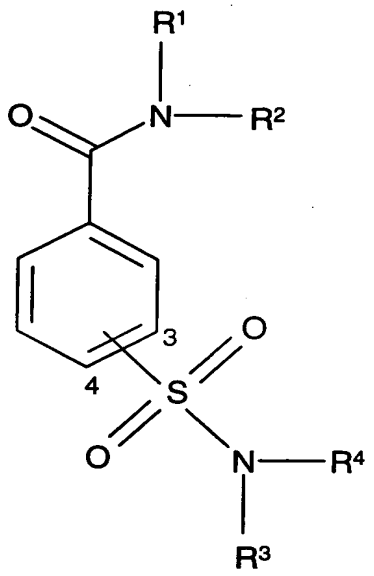
It will be appreciated that the compounds of the invention can contain one or more asymmetric carbon atom which gives rise to enantiomers. The compounds can be prepared as racemates or can be made from enantiomeric intermediates. Both racemates and enantiomers form part of the present invention.

It will also be understood that salts of the compounds of the invention can be prepared and such salts are included in the invention. They can be any of the well known acid addition salts. Acid addition salts are preferably the pharmaceutically acceptable non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example glycollic, maleic, fumaric, malic,oxalic, tartaric, citric, salicylic or o-acetoxybenzoic acids, or organic sulfonic acids, methane sulfonic, 2-hydroxyethane sulfonic, toluene-p-sulfonic or naphthalene-2-sulfonic acids.

In addition to pharmaceutically-acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the

preparation of other, for example pharmaceutically-acceptable, salts, or are useful for identification, characterisation or purification.

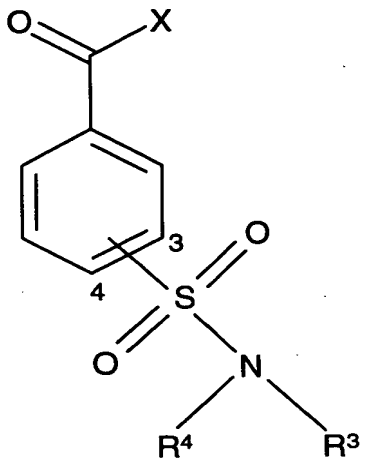
The invention includes a process for producing the compounds of formula (I) above which comprises reducing a compound of the fomula:



(II)

The reaction is preferably carried out in an organic solvent, for example, at a temperature of 0° C. to 100° C., employing a reducing agent, for example lithium aluminium hydride.

Compounds of formula (II) can readily be prepared by conventional methods, for example, by reacting a compound of the formula:



(III)

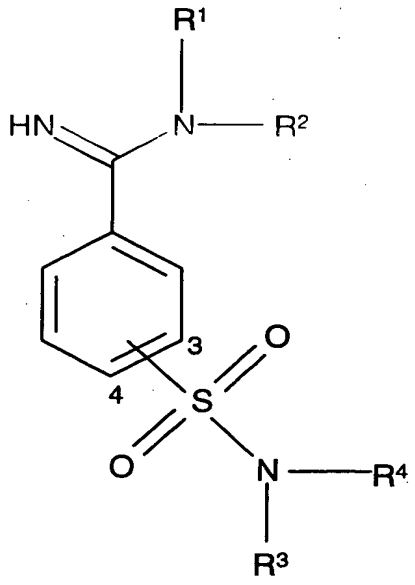
where X is a leaving group such as, for example, halo or hydroxy, with an amine of the formula HNR^1R^2.

The reaction is preferably carried out in an organic solvent such as, for example, chloroform or acetonitrile, at a temperature of from 0° C. to 100° C. such as, for example, ambient temperature.

Intermediate compounds of formula (III) are known in the art and can be readily prepared by known methods. When an acid halide is employed (X is halo such as, for example, chloro), the reaction is preferably carried out

in the presence of a solid phase scavenger to absorb the acid liberated by the reaction. When the free acid is employed (X is hydroxy), a condensing reagent such as, for example, dimethylaminopropyl-ethylcarbodiimide can be employed.

A further route to the compounds of the invention, which is also included in the invention, involves the reduction of the imine corresponding to the compound of formula (III):



(IV)

employing a reducing agent as, for example, sodium borohydride. Compounds of formula (IV) can readily be prepared by reacting an amine of formula R^1R^2NH with the

appropriate benzaldehyde derivative, which can, in its turn, be prepared by reducing the corresponding benzoic acid derivative to the alcohol, followed by oxidation to the required benzaldehyde intermediate.

Amine reactants of the formula HNR^1R^2 are well known and can be readily prepared by known methods. Those in which R^2 is $-(CH_2)_2NR^5R^6$ can, for example, be prepared by reductive amination, that is, by reacting the appropriate diamine with an aldehyde in reducing conditions.

Alternatively, compounds of formula (I) in which R^2 is $-(CH_2)_2NR^5R^6$ can be prepared by alkylation of the corresponding compound of formula (I) in which R^1 is hydrogen.

As mentioned above, the compounds of the invention are active in tests that indicate their utility in the treatment of diseases of the central nervous system. The compounds modulate the activity of calcium channels and, in particular, they block voltage sensitive calcium channels as determined in a test based on Boot J. R., et al., Specificity of autoantibodies in the Lambert-

Eaton Myasthenic Syndrome, Ann NY Acad. Sci. (1997), in which measurements of calcium flux using calcium sensitive dyes are made. Compounds described in the following Examples were found to inhibit voltage-dependent calcium channels in cloned human cell lines expressing specific voltage-dependent calcium channels with an IC_{50} of less than 10 μM.

The compounds of the invention are thus indicated for use in the treatment of anoxia, ischaemia, stroke and heart failure, migraine, diabetes, cognitive impairment, pain, epilepsy, traumatic head or spinal injury, AIDS related dementia and blindness, amnesia, neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases and age-related memory disorders, Down's syndrome, mood disorders, drug or alcohol addition withdrawal, nausea from chemotherapy, and carbon monoxide or cyanide poisoning.

The invention also includes a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in association with the compound of the invention or a pharmaceutically acceptable salt or ester thereof.

The compound may be administered by various routes, for example by the oral or rectal route, topically or parenterally, for example by injection or infusion, being usually employed in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, ointments containing, for example, up to 10% by weight of the compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydrobenzoate, talc magnesium stearate and mineral oil.

The compositions of the injection may, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Where the compositions are formulated in unit dosage form, it is preferred that each unit dosage form contains from 5 mg to 500 mg. The term 'unit dosage form' refers to physically discrete units suitable as unit dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier.

The active compound is effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.5 to 300 mg/kg, more usually in the range of from 5 to 100 mg/kg. However, it will be understood that the amount administered will be determined by the physician in the light of the relevant circumstances including the conditions to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The invention is illustrated by the following Preparations and Examples.

EXAMPLE 1

4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid

To a stirred solution of di-n-propylamine (3.03 g, 0.03 mole) in dry tetrahydrofuran (20 ml) at 0° C. (ice/salt bath), was added 4-chlorosulfonylbenzoic acid (2.2 g, 0.01 mole). Stirring was continued for 1 hour. Ice water was added cautiously and the reaction made acid with 2NHCl. The 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid was collected by filtration as a white solid which was dried *in vacuo* at 40° C.

EXAMPLE 2

4-[(N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide

To a solution of 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid (2.85 g, 0.01 mole) in dry dichloromethane

(ml) at 0° C. was added oxalyl chloride (2.54 g, 0.02 mole) and dimethylformamide (4 drops). The reaction mixture was stirred for 2 hours. The reaction was evaporated to dryness *in vacuo*. The resulting acid chloride was added to a stirred solution of *p*-methoxybenzylamine (1.51 g, 0.011 mole) and triethylamine (1.11 g, 0.011 mole) in dry tetrahydrofuran (25 ml) at 0-5° C. After stirring for 4 hours the reaction was poured into ice water and extracted with ethyl acetate. The solvent was washed with brine, dried and evaporated to dryness *in vacuo*. Chromatography on flash silica using 10% ethyl acetate/dichloromethane gave 4-{(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide as a white solid. M.p. 132-134° C.

EXAMPLE 3

N,N-di-n-propyl-4-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide

To a stirred solution of 4-[(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide(1.87g, 4.62mmole) in dry ether (50ml) was added a solution of 2M lithium aluminium hydride in tetrahydrofuran (4.63ml,

9.24mmole). The reaction was heated at reflux for 2 hours. After cooling to room temperature water (1ml) was added dropwise with caution followed by 2NNaOH (1ml). When gas evolution ceased the reaction mixture was filtered through a pad of celite which was well washed with ether. After removal of the solvent *in-vacuo* the product was purified by chromatography on flash silica eluting with 10% methanol/ethyl acetate. The resulting amine was converted to the maleic acid salt and re-crystallised from ethanol/ether to give *N,N*-di-n-propyl-4-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide maleate. mp. 133-135°C

Similarly prepared were:

N,N-di-n-propyl-3-{[(4-methoxybenzyl)amino]methyl} benzenesulfonamide maleate. mp. 160-162°C

N,N-di-n-propyl-4-{[(3,4-dimethoxyphenethyl) amino]methyl}benzenesulfonamide maleate. mp. 130-132°C

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl) amino]methyl}benzenesulfonamide maleate. mp. 169-171°C

N-(3,3-dimethylpiperidino)-4-{[(4-fluorobenzyl) amino]methyl}benzenesulfonamide maleate. mp. 196-198°C

N,N-di-n-propyl-3-{[(4-fluorobenzyl)amino]methyl} benzenesulfonamide maleate. mp. 168-170°C

N-phenyl-*N*-n-propyl-4-{[dimethylamino]methyl}

benzenesulfonamide maleate. mp. 154-156°C

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl)-N-methylamino]methyl}benzenesulfonamide maleate. Mass spectrum:MH^+=405 (TSP+)

N-(3,3-dimethylpiperidino)-3-{[(4-fluorobenzyl)-N-benzylamino]methyl}benzenesulfonamide maleate. mp. 183-185°C

N-phenyl-*N*-methyl-3-{[(4-fluorobenzyl)amino]methyl} benzenesulfonamide maleate. mp. 194-196°C

N-phenyl-*N*-n-butyl-4-{[hexylamino]methyl} benzenesulfonamide maleate. mp. 106-108°C

N-(3-ethylpiperidino)-3-{[(4-fluorobenzyl)amino] methyl}benzenesulfonamide maleate. mp. 140-142°C

N-(3,3-dimethylpiperidino)-3-{[(cyclohexylmethyl) amino]methyl}benzenesulfonamide hydrochloride. mp. 147-149°C

N-(3-methylpiperidino)-4-{[(4-chlorophenethyl)amino] methyl}benzenesulfonamide maleate. mp. 176-178°C

N-(3-methylpiperidino)-4-{[(4-chlorophenethyl)-N-methylamino]methyl}benzenesulfonamide maleate. mp. 168-170°C

3-{[[2-(dimethylamino)ethyl](4-fluorobenzyl) amino]methyl}-*N*-3,3-dimethylpiperidino-benzenesulfonamide maleate as an oil. Mass spectrum(MH^+=462(10%)) (TSP+)

3-{[[2-(dimethylamino)ethyl](cyclohexylmethyl) amino]methyl}-*N*-3,3-dimethylpiperidino-benzenesulfonamide maleate. mp. 149-151°C

EXAMPLE 4

4-{[[2-(piperidino)ethyl](2-[3,4-dimethoxy]phenylethyl)amino]methyl}-*N*,*N*-di-n-propylbenzene sulfonamide dihydrochloride

To solution of *N*,*N*-di-n-propyl-4-{[(3,4-dimethoxyphenethyl)amino]methyl}benzene sulfonamide(550 mg, 1mmole) in dry acetonitrile (100ml) was added sodium carbonate (440mg, 4.4mmole), potassium iodide (166mg, 1mmole) and 2-chloroethylpiperidine hydrochloride (184mg, 1mmole). The reaction was stirred and heated at reflux for 18 hours. The reaction was poured into ice water and extracted with ethyl acetate, washed with brine, dried and evaporated to dryness *in-vacuo*. Chromatography on flash silica by elution with 10%methanol/dichloromethane gave 4-{[[2-(piperidino)ethyl](2-[3,4-dimethoxy]phenylethyl)amino] methyl}-*N*,*N*-di-n-propylbenzenesulfonamide which was crystallised as its dihydrochloride salt. mp. 135-137°C

EXAMPLE 5

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(4-methylbenzyl)amine

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in methanol (0.25 ml) and a 0.1 M solution of 4-methylbenzylamine in methanol (0.25 ml) was stirred at room temperature for 1 hour. A 0.15 M solution of sodium borohydride in methanol (0.25 ml) was added and stirring continued for a further 16 hours. The mixture was then applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml). The eluate was vacuum evaporated to give the required product. (TS-MS: m/z 387, $[M+H]^+$).

The following compounds were similarly prepared (mass spectrum values are given in brackets).

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(4-methylpiperazin-1-yl)propyl]amine (423)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-morpholin-4-ylpropyl)amine (410)

N-(4-chlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (407/408)

N-(cyclohexylmethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (379)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(1*H*-imidazol-1-yl)propyl]amine (391)

N-butyl-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (339)

N-(*tert*-butyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (339)

N-(2-chlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (407/408)

N-(4-chlorophenethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (421/422)

N-(2-chlorophenethyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (421/422)

N-(2,4-dichlorobenzyl)-*N*-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amine (442)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-isopentylamine (353)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-methoxypropyl)amine (355)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(2-methylbenzyl)amine (387)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(3-methylcyclohexyl)amine (379)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-hexylamine (367)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-propylamine (325)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(4-methylphenethyl)amine (401)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(trifluoromethyl)benzyl]amine (441)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-[3-(trifluoromethyl)phenethyl]amine (455)

EXAMPLE 6

1-({3-[(4-benzylpiperidin-1-yl)methyl]phenyl}sulfonyl)-3,3-dimethylpiperidine

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in dichloromethane (0.25 ml), a 0.1 M solution of 4-benzylpiperidine in dichloromethane (0.25 ml) and a 0.15 M solution of sodium tri-acetoxyborohydride in dichloromethane (0.25 ml) was stirred at room temperature for 22 hours. Methanol (1 ml) was added and the mixture applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml). The eluate was vacuum evaporated to give the required product. (TS-MS: m/z 441, $[M+H]^+$).

The following compounds were similarly prepared (mass spectrum values are given in brackets).

2-(butyl{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amino)ethan-1-ol (383)

2-(benzyl{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}amino)ethan-1-ol (417)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*,*N*-bis(2-methoxyethyl)amine (399)

1-(3,4-dichlorophenyl)-4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine (497)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-ethyl-*N*-(pyridin-4-ylmethyl)amine (402)

1-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-4-(4-fluorophenyl)piperazine (446)

4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine-1-carbaldehyde (380)

4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}morpholine (353)

1-[4-(4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazin-1-yl)phenyl]ethan-1-one (470)

3,3-dimethyl-1-{[3-(pyrrolidin-1-ylmethyl)phenyl]sulfonyl}piperidine (337)

2-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-1,2,3,4-tetrahydroisoquinoline (399)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*,*N*-dipropylamine (367)

1-benzhydryl-4-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperazine (518)

N-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}-*N*-(2-methoxyethyl)-*N*-propylamine (383)

EXAMPLE 7

1-{3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzyl}piperidine-4-carboxamide

A mixture of a 0.15 M solution of 3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]benzaldehyde in methanol (0.25 ml), a 0.1 M solution of piperidine-4-carboxamide in methanol/acetic acid 4:1 v/v (0.25 ml) and a 0.15 M solution of sodium cyanoborohydride in methanol (0.25 ml) was stirred at room temperature for 18 hours. The mixture applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge and washed through with methanol (2.5 ml). The cartridge was then eluted with a 2 M solution of ammonia in methanol (2.5 ml) and the eluate vacuum evaporated. The residue was dissolved in chloroform (2 ml) and the solution added to isocyanatomethyl-polystyrene (loading 1 mmole/g, 100 mg). The suspension was shaken at room temperature for 16 hours, then filtered. The resin was washed with chloroform (2 x 2 ml) and the combined filtrates vacuum evaporated to give the required product. (TS-MS: m/z 394, $[M+H]^+$).

The following Examples illustrate typical formulations containing a compound of the invention.

EXAMPLE 8

Tablets each containing 10 mg of active ingredient are made up as follows:

Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

EXAMPLE 9

Capsules each containing 20 mg of active ingredient are made as follows:

Active ingredient	20 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 10

Capsules each containing 20 mg of medicament are made as follows:

Active ingredient	20 mg
Lactose	171 mg
Sodium lauryl sulphate	2 mg
Sodium starch glycollate	6 mg
Magnesium stearate	1 mg
	200 mg

The active ingredient, lactose, sodium lauryl sulphate and sodium starch glycollate are mixed thoroughly. The blend is mixed with the magnesium stearate and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 11

Tablets each containing 20 mg and medicaments are made as follows:

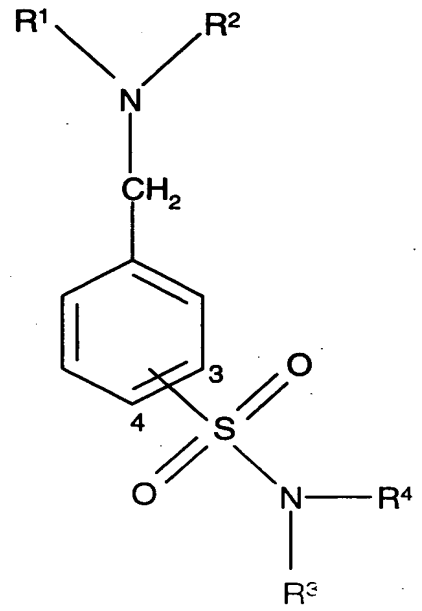
Active ingredient	20 mg
Lactose	103 mg
Microcrystalline cellulose	150 mg
Hydroxypropylmethylcellulose	15 mg
Sodium starch glycollate	9 mg
Magnesium stearate	3 mg
	300 mg

The active ingredient, lactose, microcrystalline cellulose, sodium starch glycollate and hydroxypropylmethylcellulose are passed through a sieve and blended together. Water is added to the blended powders to form a damp mass. The damp mass is passed

through a coarse screen, dried, then re-screened. The dried granules are mixed with the magnesium stearate and compressed into tablets of 300 mg weight.

CLAIMS

1. A compound of the formula



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted

phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group;

or a salt thereof.

2. A compound according to Claim 1 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with

the nitrogen atom to which they are attached, form a carbocyclic group.

3. A compound according to Claim 2 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen.

4. A compound according to Claim 3 in which R^1 is hydrogen, R^2 is optionally substituted phenyl-C_{1-4} alkyl and R^3 and R^4 are C_{1-6} alkyl.

5. A compound according to Claim 1 in which R^2 is $-(CH_2)_2NR^5R^6$.

6. A compound according to Claim 1 or 5 in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

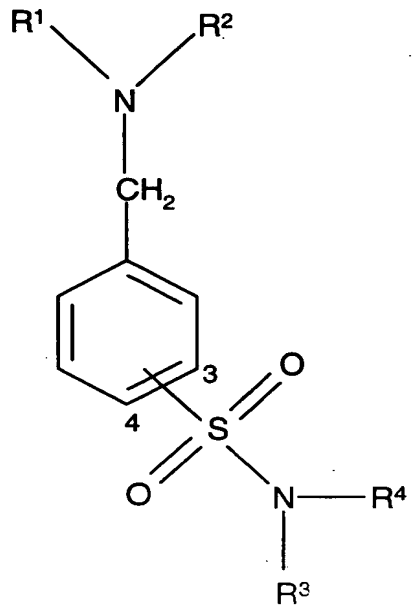
7. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 6 or a pharmaceutically acceptable salt thereof, together with a diluent or carrier therefor.

8. A compound according to any of Claims 1 to 6, for use as a pharmaceutical.

9. Use of a compound according to any of Claims 1 to 6, in the manufacture of a medicament for treating a disease of the central nervous system.

ABSTRACT

A pharmaceutical compound of the formula



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or

$-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group;

or a salt thereof.

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Agent : El. Lilly & Co Ltd

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